

I Claim:

1. A controlled release central nervous system stimulant formulation comprising:
 - (a) a core comprising of:
 - (i) a central nervous system stimulant;
 - (ii) a binder;
 - (iii) a diluent; and
 - (b) a controlled release coating comprising;
 - (i) at least one enteric polymer;
 - (ii) a plasticizer; and
 - (iii) optionally a anti-sticking agent; and
 - (c) an immediate release drug layer comprising;
 - (i) a central nervous system stimulant;
 - (ii) a binder; and
 - (iii) optionally a stabilizer;
 - (d) optionally an overcoat comprising;
 - (a) a coating agent.
2. A controlled release formulation as defined in claim 1 wherein the central nervous system stimulant is methylphenidate or a pharmaceutically acceptable salt or isomer thereof.
3. A controlled release formulation as defined in claim 1 where the diluent is selected from the group consisting of sugars, starches or vegetable oils, lactose monohydrate, calcium phosphate, dextrin, dextrose, maltitol, maltose, starch, sucrose or talc.
4. A controlled release formulation as defined in claim 1 wherein said diluent comprises lactose monohydrate.
5. A controlled release formulation as defined in claim 1 wherein the binder in the core is a hydrogel forming polymer.

- 5 6. A controlled release formulation as defined in claim 1 where the binder in the core is selected from the group consisting of methyl cellulose, hydroxymethyl cellulose, polyvinyl pyrrolidone, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene oxides, gums, acrylate polymers and methacrylate polymers.
7. A controlled release formulation as defined in claim 1 wherein the binder in the core is hydroxypropyl methylcellulose.
- 10 8. A controlled release formulation as defined in claim 1 where the anti-sticking agent is not optional and is selected from the group consisting of talc, glyceryl monostearates, calcium stearate, magnesium stearate, stearic acid, glyceryl behenate, and polyethylene glycol.
- 15 9. A controlled release formulation as defined in claim 1 wherein said anti-sticking agent comprises colloidal silicon dioxide and magnesium stearate.
- 20 10. A controlled release formulation as defined in claim 1 wherein the enteric polymer is selected from a group consisting of zein, methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate trimellitate, shellac, polyvinyl acetate phthalate or mixtures thereof.
- 25 11. A controlled release formulation as defined in claim 1 wherein the enteric coating polymer comprises a mixture of methacrylic acid copolymer and zein.
- 30 12. A controlled release formulation as defined in claim 1 wherein the plasticizer is selected from a group consisting of acetyltributyl citrate, triacetin, acetylated monoglyceride, coconut oil, poloxamer, acetyltriethyl citrate, glycerin sorbitol, diethyloxalate, diethylmalate, diethylfumerate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylphthalate, dibutylsebacate, triethyl citrate, tributylcitrate, glyceroltributyrate, polyethylene glycol, propylene glycol and mixtures thereof.
13. A controlled release formulation as defined in claim 1 wherein the plasticizer is

acetyltributyl citrate.

14. A controlled release formulation as defined in claim 1 wherein the anti-sticking agent is selected from a group consisting of talc, colloidal silica dioxide,
5 magnesium stearate, magnesium silicate, glyceryl monostearates, calcium stearate or steric acid.

15. A controlled release formulation as defined in claim 1 wherein the anti-sticking agent is talc.

10 16. A controlled release formulation as defined in claim 1 wherein the binder employed in the immediate release drug layer is hydroxypropyl methylcellulose.

15 17. A controlled release formulation as defined in claim 1 wherein the immediate release drug layer comprising said central nervous system stimulant reaches a peak blood plasma level in less than 3 hours and said stimulant blood plasma level declines in less than 5 hours.

20 18. The controlled release methylphenidate formulation of claim 17 wherein a second dose of stimulant reaches a peak blood plasma level of about 7.2 ng/ml in about 7 to 9 hours and said stimulant blood plasma level declines to about 1.4 ng/ml in about 14 to 18 hours.

25 19. A controlled release pharmaceutical dosage formulation for oral administration comprising a core with a central nervous system stimulant, an enteric coating surrounding the core and an immediate release layer comprising a central nervous system stimulant and a stabilizer, wherein the formulation when administered to humans exhibits (a) a maximum plasma concentration up to about 20 ng/ml; (b) an AUC₀₋₂₄ up to about 200 ng/ml; (c) a T_{max2} of about 3 to about 12 hours.

30 20. The controlled release pharmaceutical dosage formulation as defined in Claim 19 wherein the formulation when administered to humans exhibits (a) a maximum plasma concentration of about 3 to about 20 ng/ml; (b) an AUC₀₋₂₄ of about 30 to about 200 (ng hr)/ml; and (c) a T_{max2} of about 3 to about 12 hours.

21. A controlled release formulation consisting essentially of:

(a) a core consisting essentially of:

(i) 5-40 weight percent of a central nervous stimulant;

(ii) 3-40 weight percent of a binder ; and

(iii) 25-90 weight percent of a diluent ; and

(iv) 0.1-10 weight percent anti-sticking agent; and

(b) a controlled release coating consisting essentially of;

(i) 10-85 weight percent based upon the total weight of the

controlled release coating of an enteric polymer;

(ii) 0.5-15 weight percent based upon the total weight of the

controlled release coating of a plasticizer; and

(iii) 10-70 weight percent based upon the total weight of the

controlled release coating of an anti-sticking agent; and

(c) an immediate release drug layer consisting essentially of;

(a) 30-60 weight percent based upon the total weight of the immediate

release coating of a central nervous system stimulant; and

(b) 40-70 weight percent based upon the total weight of the immediate

release layer of a binder; and

(c) 0.005- 5 weight percent based upon the total weight of the

immediate release layer of a stabilizer.

22. A controlled release formulation as defined in claim 21 wherein:

(a) the core consisting essentially of:

(i) 10-25 weight percent of a central nervous stimulant;

(ii) 3-40 weight percent of a binder; and

(iii) 45-85 weight percent of a diluent; and

(iv) 0.5-5 weight percent anti-sticking agent; and

(b) a controlled release coating consisting essentially of;

(i) 45-80 weight percent based upon the total weight of the

controlled release coating of an enteric polymer;

(ii) 1- 5 weight percent based upon the total weight of the controlled

release coating of a plasticizer; and

(iii) 20-60 weight percent based upon the total weight of the

controlled release coating of an anti-sticking agent; and

(c) an immediate release drug layer consisting essentially of;

(a) 40-50 weight percent based upon the total weight of the immediate release coating of a central nervous system stimulant; and

5 (b) 45-60 weight percent based upon the total weight of the immediate release layer of a binder; and

(c) 0.01-2 weight percent based upon the total weight of the immediate release layer of a stabilizer.

10 23. A controlled release formulation as defined in claim 22 wherein the central nervous stimulant is methylphenidate or a pharmaceutically acceptable salt or isomer thereof.

15 24. A controlled release formulation as defined in claim 22 wherein the enteric polymers comprises a mixture of methacrylic acid copolymer and zein.

20 25. A controlled release pharmaceutical dosage formulation as defined in claim 22 wherein the formulation when administered to humans exhibits (a) a maximum plasma concentration up to about 20 ng/ml; (b) an AUC₀₋₂₄ up to about 200 ng/ml; (c) a T_{max} of about 3 to about 12 hours.

25 26. A controlled release pharmaceutical dosage formulation as defined in claim 22 wherein the formulation when administered to humans exhibits (a) a maximum plasma concentration of about 3 to about 20 ng/ml; (b) an AUC₀₋₂₄ of about 30 to about 200 (ng hr)/ml; and (c) a T_{max2} of about 3 to about 12 hours.

30 27. The controlled-release pharmaceutical dosage formulation as defined in Claim 22 wherein the formulation when administered to humans exhibits plasma peaks and troughs of the delivered active ingredient similar to those experienced in multiple dosing regimens are present.

28. The controlled-release pharmaceutical dosage formulation as defined in Claim 22 wherein the formulation when administered to humans exhibits a plasma peak for the immediate release layer (T_{max1}) between 1 and 5 hours, a plasma peak for the

controlled release core ($T_{\max 2}$) between 4 and 12 hours, and a plasma trough (T_{\min}) between 2 and 7 hours in between the two peak plasma levels.

- 5 29. A controlled release pharmaceutical dosage formulation as defined in claim 22 wherein the formulation when administered to humans provides a T_{\max} from about 3 to about 12 hours.